ORGANIC LETTERS

2009
Vol. 11, No. 2
437−440

Asymmetric Michael Addition Mediated by Novel Cinchona Alkaloid-Derived Bifunctional Catalysts Containing Sulfonamides

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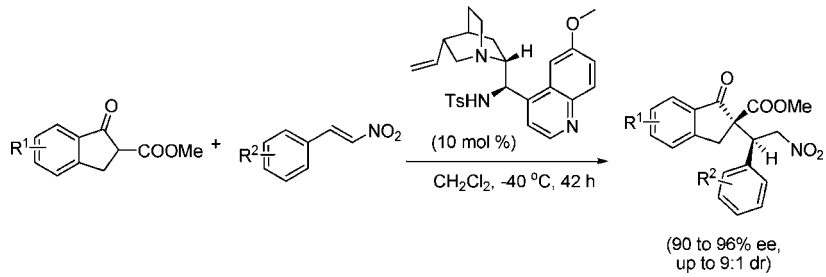
Received October 28, 2008

ABSTRACT



Novel cinchona alkaloid-derived bifunctional organocatalysts containing sulfonamide groups were utilized to promote Michael addition of bicyclic α-substituted *β*-ketoesters to nitroolefins. The desired Michael adducts with all-carbon quaternary centers were constructed in high yield and with excellent enantioselectivity, demonstrating the great potential of cinchona alkaloid-derived sulfonamides in asymmetric catalysis.

The past two decades have witnessed a terrific advancement of chiral bifunctional catalysts.[1] Over the years, chemists have designed and developed many elegant and remarkably effective bifunctional catalytic systems for asymmetric synthesis, such as Corey's CBS catalysts,[2] Noyori's DAIB for dialkyl zinc addition,[3] Shibasaki's hetero- and homobimetallic catalysts,[4] Jacobsen's metal-salen complexes,[5] and Trost's dinuclear zinc complex,[6] among others.

Asymmetric organocatalysis has progressed astonishingly in the past few years,[7] and many impressive bifunctional organocatalysts have emerged. In particular, the utilization of thiourea in bifunctional oragnocatalysts has been shown to be extremely effective,[8] presumably due to the favorable

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(1) For excellent reviews on bifunctional catalysts and multiple activations, see: (a) Steinhagen, H.; Helmchen, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 2339. (b) Wuest, J. D. *Acc. Chem. Res.* **1999**, *32*, 81. (c) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865. (d) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (e) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. (f) Muñiz, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6622. (g) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924.

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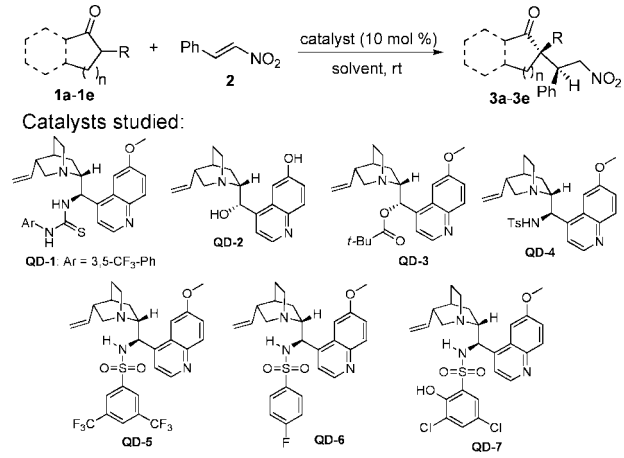
10.1021/ol802486m CCC: $40.75
Published on Web 12/10/2008

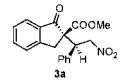
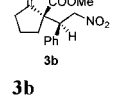
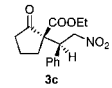
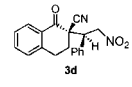
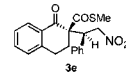
double-hydrogen-bonding interactions between thiourea moieties and the substrates. Very recently, Rawal and co-workers disclosed the use of a novel cinchona alkaloid-based squaramide as an effective hydrogen bond donor catalyst for the conjugate addition of 1,3-dicarbonyl compounds to nitroolefins.[9] *N*-Sulfonamides, containing an acidic hydrogen, represent a versatile structural scaffold that can be used for fine-tuning the structures of organocatalysts. Validity of single-hydrogen-bonding interactions of *N*-sulfonamide in asymmetric organocatalysis has been demonstrated recently. Wang and co-workers reported that pyrrolidine sulfonamide was an efficient catalyst in α-aminoxylation, aldol and Mannich reactions, α-sulfenylations, α-selenenylation, and Michael addition of aldehydes to nitrostyrenes.[10] Berkessel[11] and Adolfsson[12] also reported the use of proline *N*-sulfonamide catalyst in aldol and amination reactions, respectively.

Given the proven ability of thiourea-containing bifunctional catalysts and efficient catalysis involving hydrogen bonding interaction in *N*-sulfonamides, we became interested in developing novel bifunctional organocatalysts combining a tertiary amino group and *N*-sulfonamide moiety. Cinchona alkaloids are privileged organic catalysts,[13] which are remarkably effective and versatile in asymmetric catalysis;[8b,14] quinidine was therefore chosen as a chiral structural scaffold in our studies. We hypothesize that incorporating *N*-sulfonamides into quinidine structural scaffold could result in bifunctional organocatalysts with novel and interesting activities.[15]

Construction of quaternary stereocenters is considered to be one of the most challenging tasks in organic synthesis, and significant progress has been made in this field over the years.[16] The conjugate addition of α-substituted dicarbonyl compounds to suitable acceptor represents an important

Table 1. Screening of Organocatalysts for the Asymmetric Michael Additions to Nitrostyrene **2**[a]



entry	**3**	cat.[b]	*t* (h)	yield[c] (%)	dr[d]	ee (%) (syn/anti)
1	 **3a**	QD	24	99	1:1.6	3/5
2	**3a**	Q	20	99	1:1.4	7/-1
3	**3a**	CD	20	99	1:1.6	39/-4
4	**3a**	C	20	99	1:1.6	-26/9
5	**3a**	**QD-1**	20	99	1:1.2	10/51
6	**3a**	**QD-2**	20	99	1:1.3	47/65
7	**3a**	**QD-3**	40	71	1:1.1	41/19
8	**3a**	**QD-4**	20	99	1.6:1	74/66
9[e]	**3a**	**QD-4**	22	98	2.6:1	78/60
10[f]	**3a**	**QD-4**	**48**	**98**	**5.1:1**	**92/76**
11[e]	**3a**	**QD-5**	20	95	1.8:1	64/59
12[e]	**3a**	**QD-6**	20	96	2.6:1	78/66
13[e]	**3a**	**QD-7**	20	95	1:1	9/10
14[e,f]	 **3b**	**QD-4**	40	90	>50:1	90
15[e,f]	**3b**	**QD-5**	40	92	>50:1	85
16[e,f]	**3b**	**QD-6**	40	95	>50:1	91
17[e,f]	 **3c**	**QD-6**	40	96	>50:1	90
18[e,f]	 **3d**	**QD-6**	40	83	>50:1	63
19[e,f]	**3d**	**QD-4**	40	<30	-	-
20[e,f]	 **3e**	**QD-6**	40	72	>50:1	57

[a] Reactions were performed with 0.05 mmol of **1**, 0.055 mmol of nitrostyrene, and 0.005 mmol of catalyst in 0.15 mL of toluene at room temperature, unless otherwise specified. See Supporting Inforamtion for the assignment of absolute configurations of the products. [b] QD, quinidine; Q, quinine; CD, cinchonidine; C, cinchonine. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis of the crude products. [e] Reactions were performed in CH_2Cl_2 at room temperature. [f] Reactions were performed in CH_2Cl_2 at −40 °C.

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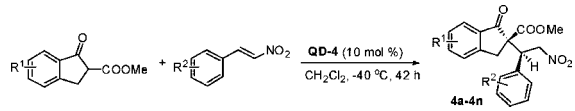
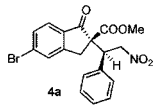
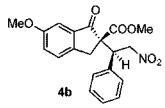
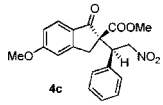
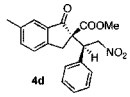
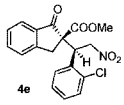
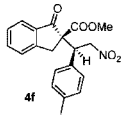
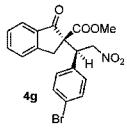
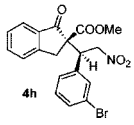
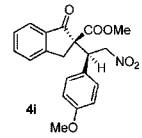
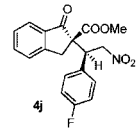
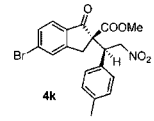
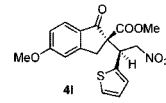
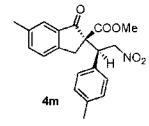
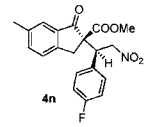
Table 2. QD-4-Catalyzed Direct Michael Addition of Bicyclic β-Ketoesters to Aryl Nitroolefins[a]



entry	product	yield[b] (%)	dr[c]	ee[d] (%)
1	 4a	98	4.1:1	92
2	 4b	99	3.3:1	90
3	 4c	98	3.3:1	95
4	 4d	97	5.9:1	93
5	 4e	98	2.4:1	93
6	 4f	97	7.1:1	93
7	 4g	98	3.5:1	93
8	 4h	96	4.4:1	95
9	 4i	97	4.6:1	96
10	 4j	98	3.5:1	94
11	 4k	98	3.3:1	90
12	 4l	98	3.1:1	94
13	 4m	98	8.8:1	91
14	 4n	99	4.1:1	94

[a] Reactions were performed with 0.05 mmol of ketoester, 0.055 mmol of nitroolefin, and 0.005 mmol of **QD-4** in 0.15 mL of CH_2Cl_2. [b] Isolated yield. [c] Determined by ^1H NMR analysis of the crude products. [d] Enantiomeric excess of the major isomer, determined by chiral HPLC analysis.

approach to generate all-carbon quaternary stereocenters. Recently, Takemoto and co-workers applied their bifunctional thiourea catalyst in enantio- and diastereoselective Michael addition of dicarbonyl compounds to nitroolefins.[17] In another elegant organocatalytic approach, Deng et al. reported the construction of quaternary stereocenters by conjugate addition of β-ketoesters mediated by cinchona alkaloid catalyst.[18] Herein, we wish to report a highly enantioselective organocatalytic Michael addition of bicyclic α-substituted β-ketoesters[19] to nitroolefins for the asymmetric construction of all-carbon quaternary stereocenters promoted by novel cinchona alkaloid-derived *N*-tosylsulfonamide-containing organocatalysts.

In our initial study, the Michael addition of α-substituted cyclic β-ketoester (**1**) to nitrostyrene (**2**) was selected as a model reaction (Table 1). Natural quinidine, quinine, cinchonidine, and cinchonine were not effective, affording products with very low enantioselectivity (entries 1−4). When quinidine-derived thiourea (**QD-1**) was used as the

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(19) Michael additions of bicyclic α-substituted β-ketoesters to nitroolefins are rare in the literature, and only a couple of examples were reported in ref 17.

catalyst, only moderate enantioselectivity was attainable (entry 5). The 6′-demethylated quinidine (**QD-2**),[20] proven to be a powerful catalyst in a number of enantioselective transformations, led to only moderate enantioselectivity (entry 6). When the C9 hydroxy function in quinidine was protected as a bulky *tert*-butyl ester, both the rate of reaction and enantioselectivity dropped (entry 7). The fact that **QD-1** and **QD-2** were better catalysts in promoting asymmetric Michael addition seemed to indicate the importance of hydrogen bonding in the chiral induction. When *N*-tosylsulfonamide-containing catalyst **QD-4** was tested, we were delighted to find the desired Michael product was obtained in quantitative yield and with good enantioselectivity (entry 8). Upon lowering the reaction temperature and performing a solvent screening, good diastereoselectivity and excellent enantioselectivity were achieved (entries 9 and 10). A number of novel quinidine-based *N*-sulfonamides were prepared and examined. Whereas **QD-6** and **QD-4** showed similar catalytic effects, catalysts **QD-5** and **QD-7** were less effective (entries 11−13). Monocyclic β-ketoester **1b** was an excellent substrate, the Michael addition of which to nitroolefin yielded adducts with exceptional diastereoselectivity and excellent enantioselectivity (entries 14−16).[21] The ester moiety in ketoester seemed to have little influence on stereoselectivity (entry 17). **QD-6** could also effect the asymmetric additions of β-ketonitrile and β-ketothioester to nitroolefin, although only modest enantioselectivities were obtained (entries 18 and 20).

After the initial screening of the catalysts and examination of different reactions, we next focused on Michael reactions involving bicyclic β-ketoesters of type **1a** as donors, since the Michael addition of such substrates to nitroolefin remained to be largely unexplored. A wide range of aryl nitroolefins and bicyclic α-substituted β-ketoesters were employed in the **QD-4**-promoted organocatalytic Michael reactions, and the Michael adducts were obtained in virtually quantitative yield, with moderate to good diastereoselectivity and excellent enantioselectivity (Table 2).

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(21) The observed diasteroselectivity for this type of substrates is consistent with the similar examples reported in ref 18a.

On the basis of the observed reactivity and experimental results of the described reactions, we propose that the reaction proceeds via a dual activation model. As shown in Figure 1, the ketoester and nitroolefin may get activated simultaneously through their interactions with cinchona alkaloid-derived sulfonamides.

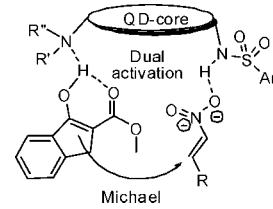

Figure 1. Proposed dual activation in the Michael addition.

In summary, new bifunctional organocatalysts (**QD-4** to **QD-7**) derived from cinchona alkaloid incorporating *N*-sulfonamide were prepared. **QD-4** was utilized to promote the Michael addition of bicyclic α-substituted β-ketoesters to nitroolefins, yielding highly functionalized all-carbon quaternary Michael adducts with excellent enantioselectivity. The studies carried out in this report demonstrated that single-hydrogen-bonding activation is a powerful approach in asymmetric organocatalysis, and we believe this finding can contribute to the design of novel bifunctional catalysts. Further development of relevant catalytic systems and the full extension of the scope of this chemistry are in progress in our laboratory and will be reported in due course.

Acknowledgment. We thank the National University of Singapore and the Ministry of Education (MOE) of Singapore (R-143-000-362-112) for generous financial support.

Supporting Information Available: Preparation and characterization of novel cinchona-based sulfonamide catalysts, representative experimental procedure for Michael addition to nitroolefins, HPLC chromatogram, and analytical data and NMR spectra of the Michael adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802486M